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Health and Environmental Effects Profile for Toluidines

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16. ABSTRACT

The Health and Environmental Effects Profile for Toluidines was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. o-Toluidine and p-toluidine have been evaluated as carcinogens. The human carcinogen potency factor (q_1^*) for o-Toluidine is 2.4×10^{-1} $(mg/kg\ bw/day)^{-1}$ and for p-toluidine is 1.9×10^{-1} $(mg/kg\ bw/day)^{-1}$ for oral exposure.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for m-toluidine.

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HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR TOLUIDINES

ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

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LIST OF ABBREVIATIONS

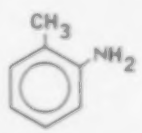
COD	Chemical oxygen demand
DNA	Deoxyribonucleic acid
LC_{50}	Concentration lethal to 50% of recipients
LD_{50}	Dose lethal to 50% of recipients
ppb	Parts per billion
ppm	Parts per million
SCE	Sister chromatid exchange
TLV	Threshold limit value
TOC	Total organic carbon
TWA	Time-weighted average
UV	Ultraviolet

1. INTRODUCTION

Toluidines are a class of compounds obtained by the substitution of the NH_2 group at different positions of a toluene ring structure. The three possible isomers of this substitution are o-toluidine, m-toluidine and p-toluidine. Besides the three isomers, a mixture of the three isomeric toluidines is also available in the market. This hazard profile on the toluidines attempts to discuss each toluidine individually in the following sections.

1.1. STRUCTURES AND CAS NUMBERS

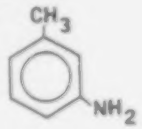
1.1.1. Structure and CAS Number for o-Toluidine. o-Toluidine, also known as 2-aminotoluene, has a molecular formula of C_7H_9N and a molecular weight of 107.2. Other synonyms for this compound are: benzenamine, 2-methyl-; 1-amino-2-methylbenzene; 2-amino-1-methylbenzene; ortho-aminotoluene; 1-methyl-2-aminobenzene; 2-methyl-1-aminobenzene; 2-methylaniline; 2-toluidine; ortho-tolylamine; ortho-methylaniline; 2-methylbenzenamine; and ortho-methylbenzenamine (IARC, 1982a). The structural formula of o-toluidine is:



The Chemical Abstract Service (CAS) Registry number for this compound is 95-53-4.

1.1.2. Structure and CAS Number for m-Toluidine. The compound m-toluidine, also known as 3-aminotoluene, has a molecular weight of 107.2. Other synonyms for this isomer are: benzenamine, 3-methyl-; 1-amino-3-methylbenzene; 3-amino-1-methylbenzene, meta-aminotoluene; 1-methyl-3-aminobenzene; 3-methyl-1-aminobenzene; 3-methylaniline; 3-toluidine; metatolylamine;

metamethylaniline; 3-methylbenzenamine; and meta-methylbenzenamine. The structural formula of m-toluidine is:



The Chemical Abstract Service (CAS) Registry number for this compound is 108-44-1.

1.1.3. Structure and CAS Number of p-Toluidine. The compound p-toluidine, also known as 4-aminotoluene, has a molecular weight of 107.2. Other synonyms for this isomer can be fashioned in accordance to the other two isomers already discussed. The structural formula of p-toluidine is:

The Chemical Abstract Service (CAS) Registry number for this compound is 106-49-0.

1.1.4. Structure and CAS Number for the Mixture. The Chemical Abstract Service Registry number for the mixture of isomers is 26915-12-8.

1.2. PHYSICAL AND CHEMICAL PROPERTIES

The physical properties of the three pure isomers are shown in Table 1-1. The physical properties of the mixture of isomers will be dependent upon the ratio in which the isomers are mixed. For a fixed ratio of isomers, the physical properties will be well-defined; however, the physical properties of a mixture having a fixed proportion of each isomer could not be found in the literature.

Chemically, the three isomers of toluidine will act as weak bases and are expected to participate in reactions involving the amino group. For example, all three compounds will form salts with strong acids and will

TABLE 1-1

A Few Selected Physical Properties of Toluidines[a]

Compound/Property	o-Toluidine	m-Toluidine	p-Toluidine
Description[b]	light yellow liquid at ambient temperature	colorless liquid at ambient temperature	white crystalline solid at room temperature
Melting point °C	-14.7	-30.4	44-45
Boiling point °C	200.2	203.3	200.5
Specific gravity	0.9984_4^{20}	0.9889_4^{20}	0.9619_4^{20}
Water solubility at 20°C	16,300 mg/ℓ[c]	15,000 mg/ℓ[c]	6500 mg/ℓ[d]
Log octanol/water partition coefficient	1.29[c]	1.40[c]	1.40[d]
Vapor pressure at 20°C	0.1 mm Hg[e]	NA	NA
Soil sorption coefficient (K_{OC}) standardized for organic matter	NA	1.41[d]	1.66[d]
Conversion factor at 20°C and 760 mm	1 ppm = 4.45 mg/m³	1 ppm = 4.45 mg/m³	1 ppm = 4.45 mg/m³
pK at pH=8 and 20°C[f]	9.59	9.33	8.93

[a]Weast, 1980 unless otherwise stated

[b]Northcott, 1978

[c]Chiou et al., 1982

[d]Briggs, 1981

[e]Verschueren, 1983

[f]Korenman and Kochetkova, 1968

NA = Not available

participate in diazotization reaction. In fact, the latter reaction is the main reason for their usefulness in the manufacture of dyes. The conventional chemical reactions which usually are conducted at relatively high concentrations may not be relevant at ambient environmental conditions. The possible environmental reactions of these chemicals are discussed in Chapter 2.

1.3. PRODUCTION DATA

1.3.1. Production Data for o-Toluidine. Both the TSCA file and the SRI directory (SRI, 1983) list DuPont Co., Inc., Deepwater, NJ, and First Mississippi Corp., Pascagoula, MS, as the two producers of this chemical in United States. The TSCA file estimates the production of o-toluidine by the latter company at 1-10 million pounds/year. No production data for DuPont Co. are available. Imports of o-toluidine in the United States in 1979 were reported to be ~0.6 million tons, a quantity much larger than had been reported in previous years (IARC, 1982a).

1.3.2. Production Data for m-Toluidine. The TSCA Production File indicates four domestic producers of m-toluidine. The plant information for one of these remains confidential. The three other plants are: DuPont Co., Inc., Deepwater, NJ; BASF Wyandotte Corp., Geismar, LA; and Union Carbide Corp., Institute, WV. The Directory of Chemical Producers (SRI, 1983) lists DuPont as the sole U.S. manufacturer of this chemical as of January, 1983. The present annual production data for this compound are not available.

1.3.3. Production Data for p-Toluidine. According to the TSCA Production File, only one United States company, DuPont Co., Inc., Deepwater, NJ, produced this chemical before 1977. The Directory of Chemical Producers

(SRI, 1983) lists an additional company, First Mississippi Corp., Pascagoula, MS, as the second United States producer of this chemical as of January, 1983. Information regarding its annual production volume was not available.

1.4. USE DATA

The chemical o-toluidine is used primarily as an intermediate in the manufacture of dyes, rubber vulcanization accelerators, and hypnotic and anaesthetic pharmaceuticals; in the production of a pesticide (siduron); and as an intermediate in the synthesis of organic chemicals (IARC, 1982a).

The primary uses of m-toluidine are in the preparation of dyes and as an intermediate in the synthesis of organic chemicals (Hawley, 1981).

The three main uses of p-toluidine are in the manufacture of dyes, in the synthesis of organic chemicals and as a reagent for lignin, nitrile and phloroglucinol (Hawley, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

2.1. O-TOLUIDINE

The fate of o-toluidine in aquatic media with respect to biodegradation by activated sludge has been studied by several investigators. Aniline acclimated activated sludge was found to completely biodegrade o-toluidine in <8 days (Malaney, 1960). Similarly, Pitter and Richtrova (1974) found that aniline-acclimated activated sludge readily degraded o-toluidine. Activated sludge acclimated with p-nitroaniline was also found to degrade o-toluidine (Udod, 1973). Udod et al. (1972) isolated 12 species of Pseudomonas and 15 species of bacillus from nitroaniline-acclimated sludge and demonstrated that these isolated microorganisms could easily biodegrade o-toluidine.

The biodegradation of o-toluidine can also be accomplished by activated sludge without prior acclimatization. For example, it has been shown by various investigators that o-toluidine is quite biodegradable with activated sludge and ambient water temperature and pH (Sasaki, 1978; Kitano, 1978; Matsui et al., 1975). Matsui et al. (1975) demonstrated that 92% COD removal and 83% TOC removal from aqueous solutions containing o-toluidine can take place with activated sludge in 24 hours. Pitter (1976) determined the rate of biodegradation of o-toluidine by activated sludge to be 15.1 mg COD g^{-1} hr^{-1}, a rate that was slower than the degradation rate of the m- and p-isomers. From the O_2 uptake study, Marion and Malaney (1964) concluded, however, that o-toluidine would not significantly biodegrade by activated sludge in 7.5 days, possibly reflecting different microbial composition.

It can be concluded from the above discussion that o-toluidine may biodegrade in aquatic media with or without acclimated microorganisms. None

of the above laboratory experiments, however, reflect the situations that may be encountered for ambient aquatic media in the field. In the absence of adequate field data or the value for the rate constant of biodegradation, it is difficult to estimate the half-life of o-toluidine biodegradation in ambient aquatic media.

The fate of o-toluidine under two likely reaction conditions, direct photolytic and reaction with dissolved oxygen under sunlight, has not been fully explored. The possibility of direct photochemical degradation of aquatic m-toluidine by sunlight has been demonstrated by Kondo (1978). Similar studies for o-toluidine are not available. The reaction of gas phase o-toluidine in the presence of molecular oxygen with light of maximum wavelength of 365 nm has also been studied (Pouyet and Meallier, 1967; Meallier, 1969); however, no study relating the oxidative transformation of o-toluidine in aquatic media by sunlight and dissolved oxygen is available.

The rate of volatilization of o-toluidine from aquatic media is unknown. Considering the reasonably high water solubility and relatively low vapor pressure (see Section 1.2.), it is unlikely that volatilization will play a major role in transporting the compound from aquatic to atmospheric media. The rate of removal of this compound from aquatic phase by sorption onto particle matter in water is expected to be low to intermediate. This prediction is based on its log K_{ow} value (see Section 1.2.). A part of the compound may, however, react with the carbonyl groups of the humic substances present in aquatic media and be transformed to other chemicals with undetermined effects on the biosphere (Parris, 1980).

Little information regarding the fate of o-toluidine in the atmospheric media is available. In the presence of molecular oxygen, o-toluidine will undergo photochemical oxidation in the troposphere (Meallier, 1969; Pouyet

and Meallier, 1967). Although the photochemical oxidizability was shown to decrease in the order p- > o- > m-, the tropospheric half-life for o-toluidine due to this reaction was not determined (Meallier, 1969). No reference to another reaction that is likely to affect the atmospheric concentration of o-toluidine (for example, the reaction with peroxy radicals) could be found in the literature.

In view of the relatively low octanol/water partition coefficient, o-toluidine is not likely to be bound strongly onto the particulate matter in the atmosphere. Because of its reasonably high water solubility, the transport of atmospheric o-toluidine by both wet and dry precipitation seems likely.

The biodegradation possibility of o-toluidine in soils has been studied by several investigators. Alexander and Lustigman (1966) found that a 1% suspension of Niagara silt loam completely destroyed o-toluidine in 64 days. o-Toluidine was determined by these authors to be more resistant to biodegradation than its p- and m-isomers. Bordeleau and Bartha (1972) isolated a peroxidase from the soil fungus, G. candidum, and showed that this peroxidase biodegraded o-toluidine with the formation of azo-compounds. Medvedev and Davydov (1972) found that microbial transformation of o-toluidine in soils left very stable decomposition products that did not degrade even after 3 months.

The soil sorption of alkyl anilines was studied by Felice et al. (1982). They determined that the presence of both organic matter and crystalline mineral matter (Fe-oxides and phyllosilicates) in the soil were important for the sorption of alkyl anilines in soil. The soil pH is also important in determining the leachability of alkyl anilines from soils. At acidic pH, the amine will form salts that will ionize. Therefore, the ion-exchange

capacity of soil may be an important factor in determining leachability from acidic soils. In case of basic soil, the sorption onto organic or inorganic minerals may play an important role in determining the leachability of o-toluidine from soil.

The transport of o-toluidine from soil to the atmosphere through volatilization may not be an important process because of the relatively low vapor pressure of this compound at ambient temperature. The relatively high water solubility, however, indicates that o-toluidine may be transported from soil to surface water through rainwater washoffs.

2.2. M-TOLUIDINE

The biodegradability of m-toluidine in aquatic media has been studied by several investigators (Marion and Malaney, 1964; Malaney, 1960; Pitter, 1976; Pitter and Richtrova, 1974). These authors concluded that m-toluidine can be biodegraded both by acclimated and unacclimated activated sludge. The biodegradation of m-toluidine, however, is faster than the o- and p-isomers (Malaney, 1960). Pitter (1976) determined the rate of biodegradation of m-toluidine to be 30 mg COD g^{-1} hr^{-1}.

The fate of m-toluidine in aquatic media under photolytic conditions was studied by Kondo (1976). With a UV lamp of maximum wavelength of 250 nm, the half-life of photodegradation of m-toluidine in aquatic solution was determined to be 5.1 and 5.8 hours under shaking and standing conditions, respectively. The solar wavelengths in the troposphere, however, exceed 290 nm. In his experiments with aquatic m-toluidine solution, Kondo (1976) showed that the half-life of m-toluidine is 2.8 days when irradiated with a fluorochemical lamp of maximum wavelength of 350 nm and a range of 300-400 nm.

The other possible oxidative transformation of m-toluidine with oxygen and light (wavelength 365 nm), though observed in the vapor phase (Pouyat and Meallier, 1967; Meallier, 1969), has not been studied in the aquatic phase with realistic dissolved oxygen concentrations.

Because vapor pressure has not been determined, predicting the possibility of volatilization of this compound from aquatic media is difficult. Based on its K_{ow} and K_{oc} values, the rate of removal of this compound from aquatic phase by sorption onto particle matter in water is expected to be low to intermediate. As in the case of the o-isomer, however, m-toluidine may react with the carbonyl groups or undertake an addition reaction with quinoidal structure of the humic substances present in water and may be transformed to other chemicals with undetermined effects on the biosphere (Parris, 1980).

Like o-toluidine, m-toludine is expected to undergo photochemical oxidation in the presence of molecular oxygen present in the atmosphere. The rate of this reaction, however, is expected to be slower than the corresponding reaction with o-toluidine (Meallier, 1969; Pouyet and Meallier, 1967). The possibility of peroxy radical reaction with atmospheric m-toluidine has not been studied.

In view of the relatively low K_{ow} and K_{oc} values, m-toluidine is not likely to be bound strongly onto particulate matter in the atmosphere. Atmospheric m-toluidine, like o-toluidine, is expected to be transported to surface water and soil by both wet and dry precipitation.

Bordeleau and Bartha (1972) isolated G. candidum peroxidase from soil that was shown to biodegrade m-toluidine with the formation of azo compounds. Alexander and Lustigman (1966) found that 1% suspension of Niagara silt loam completely destroyed m-toluidine in 8 days. Using a soil profile

collected from Davies County, KY, Felice et al. (1982) showed that m-toluidine was readily metabolized by soil microorganisms within 32 days.

The soil sorption characteristic of m-toluidine is expected to be similar to that discussed for o-toluidine. In soils with high organic matter and specific crystalline mineral content, leaching of m-toluidine is expected to be retarded. With soils of acidic pH, the leaching of m-toluidine may be progressively retarded as the soil cation exchange capacity increases.

Because vapor pressure has not been determined, no prediction about the possibility of volatilization of m-toluidine from soils can be made. Based on its relatively high water solubility, however, this compound is expected to be transported from soil to surface water through runoff water.

2.3. P-TOLUIDINE

The biodegradability of p-toluidine in aquatic media has been studied by a number of investigators (Sasaki, 1978; Marion and Malaney, 1964; Kitano, 1978; Udod, 1973; Malaney, 1960; Pitter, 1976; Udod et al., 1972; Pitter and Richtrova, 1974). These authors concluded that p-toluidine can be biodegraded both by acclimated and unacclimated activated sludge and by microorganisms isolated from acclimated activated sludge. The biodegradation rate of p-toluidine was determined to be intermediate between the m- and o-isomer (Malaney, 1960; Pitter, 1976). Pitter (1976) determined the biodegradation rate of p-toluidine in aquatic solution to be 20 mg COD g^{-1} hr^{-1} with activated sludge as microbial inoculum.

Although the possibility of direct photochemical reaction of m-toluidine with sunlight and the gas phase reaction of p-toluidine in the presence of molecular oxygen with light (wavelength 365 nm) have been demonstrated (Kondo, 1978; Pouyet and Meallier, 1967; Meallier, 1969), the corresponding reactions in aquatic media have not been studied.

It is difficult to predict the possibility of volatilization of p-toluidine from aquatic media unless more data regarding at least its vapor pressure or Henry's constant value are available. Based on its K_{ow} and K_{oc} values, the compound is not expected to be significantly removed from aquatic phase by sorption onto particle matter in water. p-Toluidine may, however, react with the carbonyl group or undertake an addition reaction with quinoidal structure of the humic substances present in water and may be transformed to other chemicals with undetermined effects on the biosphere (Parris, 1980).

p-Toluidine is expected to undergo photochemical oxidation in the presence of molecular oxygen in the atmosphere (Meallier, 1969; Pouyet and Meallier, 1967). The rate for this reaction has been established to be fastest for p-toluidine compared with its other two isomers. The possibility of peroxy radical reaction with atmospheric p-toluidine has not been established.

Because of its relatively low K_{ow} and K_{oc} values, p-toluidine is not likely to be bound strongly onto particulate matter in the atmosphere. Atmospheric p-toluidine is expected to be transported to surface water and soil by both wet and dry precipitation, although the wet precipitation rate may be lower than the o- and m-isomers because of its lower water solubility compared with the other two isomers.

Using a 1% suspension of a soil (Niagara silt loam) inoculum, Alexander and Lustigman (1966) demonstrated that p-toluidine was completely destroyed in 4 days. The p-isomer was found to be more biodegradable than the other two isomers. Bordeleau and Bartha (1972) also concluded from their experiments with fungal enzymes (G. candidum) isolated from soils that the soil biodegradation of p-toluidine is faster than the other two isomers.

Medvedev and Davydov (1972) demonstrated that the biodegradation of p-toluidine in soils left very stable decomposition products.

The soil sorption characteristics of p-toluidine are expected to be similar to that of m-toluidine, although p-toluidine is expected to be more tightly bound in soils than the m-isomer (K_{oc} value of 1.66 versus 1.41). In soils with high organic matter and specific crystalline mineral content, leaching to p-toluidine is expected to be retarded because of enhanced sorption. In acidic soils, the leaching of p-toluidine may be progressively retarded as the soil cation exchange capacity increases.

No prediction about the rate of volatilization of p-toluidine from soil to the atmosphere can be made. Based on its water solubility, however, the compound is expected to be transported from soil to surface water through solubilized and particle-bound form in runoff water.

3. EXPOSURE

3.1. WATER

Toluidine and some of its specific isomers have been found in a few surface water, secondary effluents from wastewater treatment plants, in groundwater near an underground coal gasification site, and in condensate and process retort water from oil-shale retort operation. For example, Ellis et al. (1982) reported qualitatively the detection of o-toluidine in secondary effluent samples from a publicly-owned treatment works in Illinois. Similarly, Meijers and Van der Leer (1976) detected alkylaniline in the water from River Waal at Brakel, the Netherlands. The reported concentrations of toluidines in a few surface waters, groundwater, and retort water from in situ oil-shale retort operations are shown in Table 3-1. Unidentified toluidine isomers were found in the effluents from a few chemical manufacturing operations in Kingsport, TN, and Morristown, TN (Shackelford and Keith, 1976). Trace amounts of o-toluidine were found in the water from the North Sea, probably because of ocean dumping of chemical wastes (Greve, 1971), and in upper Catawba River, NC (Shackelford and Keith, 1976). All three isomers of toluidine were found in the effluent from coking works (Shackelford and Keith, 1976). o-Toluidine at a concentration of 9800 µg/kg and p-toluidine at a concentration range of 400-900 µg/kg were determined in Niagara River sediments at a depth of 9 feet, as reported in STORET.

The occurrence of any of the toluidine isomers in finished drinking water has not been reported. Therefore, it is unlikely that measurable amounts of these compounds will be ingested through drinking water.

TABLE 3-1

Concentrations of Toluidine in Aquatic Samples

Type of Sample	Source of Sample	Mean Concentration, ppb				Reference
		o-Toluidine	m-Toluidine	p-Toluidine	Unidentified Toluidine Isomers	
Surface water	River Rhine at Lobith	0.03(6)[a]	NR	0.17(56)	NR	Wegman and DeKorte, 1981
Surface water	Tributary o° Rhine (Boven Merwede)	0.07(8)	NR	0.07(42)	NR	Wegman and DeKorte, 1981
Surface water	Tributary of Rhine (Ijessel)	0.20(8)	NR	0.08(46)	NR	Wegman and DeKorte, 1981
Surface water	River Alster, Germany	-[b]	NR	NR	NR	Neurath et al., 1977
Surface water	River Au near Hetlingen, Germany	0.5[b]	NR	NR	NR	Neurath et al., 1977
Surface water	River Pinnau, Germany	0.3[b]	NR	NR	NR	Neurath et al., 1977
Groundwater	Wells from Hoe Creek in Wyoming 15 months after completion of underground coal gasification	0.06-9.2[c]	ND-3.3	0.06-9.2[c]	NR	Stuermer et al., 1982
Waste water	Process retort water from in situ oil-shale retorting process at Logan, WA	3.4 x 10°	5.2 x 10°[d]	5.2 x 10°[d]	NR	Leenheer et al., 1982
Waste water	Condensate retort water from in situ oil-shale retorting process at Logan, WA	0.2 x 10°	NR	NR	NR	Leenheer et al., 1982

[a]Values in parentheses are percent occurrence.

[b]Values are in µg/kg and may be slightly different from the given ppb values.

[c]The o- and p-isomer were not separated.

[d]The m- and p-isomer were not separated.

NR = Not reported; ND = Below the limit of detection

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3.2. FOOD

Unidentified isomers of toluidine were found at concentrations of 1.1 mg/kg in fresh kale and celery and at a level of 7.2 mg/kg in fresh carrots. In preserved vegetables, unspecified toluidine isomers at concentration levels of 0.4 and 0.2 mg/kg were reported in shelled peas and red cabbage, respectively. In addition, preserved broken beans were found to contain <0.1 mg/kg of o-toluidine (Neurath et al., 1977). Vitzthum et al. (1975) identified o-toluidine in the volatile constituents of black tea aroma. It is not possible to estimate the human exposure of toluidine through the consumption of foods with these limited data.

3.3. AIR

Although toluidine was reported in tobacco smoke (Patrianakos and Hoffman, 1976) and smoke particulates from the smoldering of polyurethane foam in air (Kuriakose and Browner, 1980), no report of its presence in ambient air could be found.

3.4. DERMAL

Pertinent data on the effects of dermal exposure to toluidine were not located in the available literature.

4. COMPOUND DISPOSITION AND PHARMACOKINETICS

4.1. ABSORPTION

Toxic and carcinogenic responses in animals fed the o-, m- and p-isomers of toluidine indicate that these compounds are absorbed through the gastrointestinal tract (Weisburger et al., 1978). Urinary excretion studies indicate that, after oral administration of 50 mg/kg of radioactively labeled o-toluidine·HCl to rats, virtually all of the dose was absorbed (Cheever et al., 1980; see Section 4.4. for details). The compound was administered in distilled water by gavage.

Dermal absorption of o-toluidine in rats has been demonstrated. High mortality and toxic effects were observed after skin painting with a 0.5% solution of o-toluidine in chloroform (Morigami and Nisimura, 1940).

4.2. DISTRIBUTION

Son et al. (1980) gave groups of two male F344 rats a single subcutaneous (s.c.) injection of 50 or 400 mg/kg o-[^{14}C-methyl]toluidine·HCl in 0.9% saline. Total urine and feces were collected 24 and 48 hours after administration. Exhaled air was monitored at 6, 18, 30 and 48 hours after administration. All rats were killed 48 hours after administration, and their livers, kidneys, lungs, spleens, colons and bladders were assayed for radioactivity. In rats given 50 mg/kg, the above organs contained the following percentages of administered radioactivity, respectively: 0.125, 0.16, 0.0035, 0.02, not done and 0.0004%. In rats given 400 mg/kg, the above organs contained 0.325, 0.055, 0.015, 0.04, 0.005 and 0.015% of the administered radioactivity, respectively.

Watanabe and Kozaki (1978) studied the plasma levels of unchanged p-toluidine with time after a bolus intravenous (i.v.) injection in rabbits. The compound (10 mg/kg in isotonic NaCl solution) was injected into the ear

vein of four male albino rabbits, and samples of blood from another ear vein were analyzed for p-toluidine plasma concentration at 5, 10, 15, 30, 60 and 120 minutes after administration. A two-compartment model was obtained from least-squares multiple regression fitting of the data. The plasma half-life of p-toluidine in the first and second phase was 4 and 21.7 minutes, respectively. An apparent volume of distribution of 0.572 ℓ/kg was extrapolated from the data.

4.3. METABOLISM

Ring hydroxylation with subsequent conjugation is the primary metabolic pathway of o-, m- and p-toluidine in the rat (Cheever et al., 1980). As reviewed by Cheever et al. (1980), a number of metabolites have been observed in a variety of species *in vivo* and *in vitro* (Table 4-1). In rats given 50 mg/kg o-[methyl ^{14}C]toluidine in distilled water by gavage, the only radiolabeled component extractable from urine before hydrolysis and for up to 72 hours after dosing was unchanged o-toluidine. Analysis of hydrolyzed urine indicated that 51.7% of the total dose was excreted as conjugated metabolites within 72 hours of dosing. These metabolites were in the form of conjugated 4-amino-3-methylphenol. Similarly, when 500 mg/kg of unlabeled o-, m- or p-toluidine was administered to rats in corn oil by gavage, unchanged toluidine and conjugates of aminomethylphenols were identified in the urine (Cheever et al., 1980).

Son et al. (1980) monitored the urine, feces and expired air of rats given a single s.c. injection of 50 or 400 mg o-[methyl ^{14}C]toluidine/kg for up to 48 hours after administration. An average of 77.2 and 83.8% of the administered radioactivity was recovered from rats given 50 and 400 mg/kg, respectively. Urine, feces and expired air collected for 48 hours from rats given 50 mg/kg accounted for 74.9, 2.1 and 0.13% of the total

TABLE 4-1

Metabolism of Toluidine Isomers[a]

Compound	Metabolite Reported	Species
ortho-Toluidine	etherial sulfate	dog
	ortho-aminobenzoic acid	rabbit rat
	4-amino-3-methylphenol	rabbit rat
meta-Toluidine	meta-Aminobenzoic acid	rat
	meta-Nitrosotoluene	dog
	4-Amino-2-methylphenol	rabbit[b] rat
	2-Amino-4-methylphenol	rat
para-Toluidine	para-toluidine-N-β-D-glucuronide	rabbit
	para-nitrosotoluene	dog
	para-aminobenzoic acid	rat[b], mouse[b]
	para-aminobenzaldehyde	rabbit[b]
	2-amino-5-methylphenol	rat

[a]Source: Cheever et al., 1980

[b]Liver microsomal incubation

dose, respectively. Urine, feces and expired air collected for 24 hours from rats given 400 mg/kg accounted for 50.4, 2.2 and 0.97% of the dose, respectively. Urine, feces and expired air collected from rats given 400 mg/kg accounted for 79.2, 3.2 and 1.4% of the dose, respectively. The urine collected for 24 hours contained ~42% of the dose as para-hydroxylated products and 2% as ortho-hydroxylated products. The small amounts of $^{14}CO_2$ observed to be exhaled indicate that the oxidation of the methyl group is a minor metabolic pathway.

Acid-conjugated urinary metabolites accounted for 51% of the total dose. These metabolites were the sulfates and glucuronides of various amino and N-acetyl cresols. The ratio of sulfates to glucuronides was ~6:1. Ether extractable urinary metabolites included unchanged o-toluidine (5.1% of total dose) and eight other metabolites (2.1% of total dose). Evidence for a double acid conjugate of 4-amino-m-cresol (the N-glucuronide of 4-amino-m-cresyl sulfate) was presented.

Watanabe and Kozaki (1978) reported identifying no metabolites of p-toluidine in the plasma of male albino rabbits given a 10 mg/kg dose by i.v. injection. Blood samples were taken up to 120 minutes after administration, and no spots corresponding to metabolites were visualized on developed thin layer chromatographic plates.

4.4. EXCRETION

The primary route of excretion of o-toluidine in the rat is urinary (Cheever et al., 1980; Son et al., 1980). Approximately 92 and 95% of the radioactivity in a 50 mg/kg oral dose of o-[methyl ^{14}C]toluidine·HCl in water was excreted in the urine after 24 and 72 hours, respectively (Cheever et al., 1980). Of the excreted radioactivity, 37.4 and 51.7% was in the

form of unchanged o-toluidine and 4-amino-3-methylphenol conjugates, respectively. Oral administration of 500 mg/kg doses of unlabeled o-, m- and p-toluidine in corn oil to rats resulted in the appearance of 21% of the o-isomer, but only 2.5% of the m- or p-isomer (unchanged) in the urine after 24 hours. Attempts to quantitate other urinary metabolites (conjugates of aminomethylphenols) failed because of decomposition problems.

Son et al. (1980) reported that 24 hours after a single s.c. dose of o-[methyl ^{14}C]toluidine in male F344 rats, 56, 2.3 and 1% of the dose appeared in the urine, feces and expired air, respectively. After 48 hours, 83.9, 3.3 and 1.4% of the dose appeared in the urine, feces and expired air, respectively. Ether extractable urinary metabolites accounted for 7.2% of the dose, and acid conjugated urinary metabolites accounted for 51% of the dose.

5. EFFECTS

5.1. CARCINOGENICITY

The carcinogenicity of o-toluidine•HCl was demonstrated in three chronic feeding studies in rats and mice (Table 5-1) (NCI, 1979; Weisburger et al., 1978; Hecht et al., 1982). Equivocal evidence of bladder cancer in o-toluidine-exposed workmen has also been reported.

In a study conducted by NCI (1979), groups of F344 rats (50 of each sex) were fed diets containing 3000 or 6000 ppm (mg/kg/diet) o-toluidine•HCl ($\geq$99% purity) for 101 or 104 weeks. Dose-related decreases in body weight gain and mortality increases were noted. Increased incidences of sarcomas, fibrosarcomas, osteosarcomas and angiosarcomas in multiple organs were noted in males [0/20 in controls, 15/50 in the low-dose group ($p=0.003$) and 37/49 in the high-dose group ($p<0.001$)]. The incidences of splenic sarcomas, osteosarcomas and angiosarcomas were increased in female rats [0/20 in controls, 9/49 in the low-dose group ($p=0.036$) and 12/49 in the high-dose group ($p=0.01$)]. Female rats also showed a dose-related increase in the incidence of transitional cell carcinoma of the urinary bladder [0/20, 9/45 ($p=0.028$), and 22/47 ($p<0.001$) for controls, low and high-dose groups, respectively)] and mammary adenomas [6/20, 20/50 and 35/49 ($p=0.002$) for control, low and high-dose groups, respectively]. Fibromas of the subcutaneous tissue were increased in male rats [0/20, 28/50 ($p<0.01$), 27/50 ($p<0.001$) for control, low and high-dose groups, respectively].

Weisburger et al. (1978) treated groups of male Charles River CD (Sprague-Dawley derived) rats with o-toluidine•HCl in the diet at two dose levels, the higher at the maximum tolerated dose and the lower at one-half that level. o-Toluidine•HCl was administered in the diet at 16,000 mg/kg for 3 months and 4000 mg/kg for 15 months to the low-dose group. Following

TABLE 5-1

Summary of Oral Carcinogenicity Data for o-Toluidine·HCl

Species/ Strain	Sex/ Number	Dose/Schedule	Duration of Treatment	Duration of Study	Target Organ	Tumor Type	Tumor Incidence (P Value)	Reference
Rat/Charles River CD	M/25	0, matched control	18 months	24 months	subcutaneous	fibromas and fibrosarcomas	0/16	Weisburger et al., 1978
					other	multiple tumors	3/16	
	M/111	0, pooled control	18 months	24 months	subcutaneous	fibromas and fibrosarcomas	18/111	Weisburger et al., 1978
					other	multiple tumors	14/111	
	M/25	8000 ppm diet x 3 months, then 4000 ppm x 15 months (233.3 mg/kg/day[a])	18 months	24 months	subcutaneous	fibromas and fibrosarcomas	18/23 ($p<0.025$) all controls	Weisburger et al., 1978
					other	multiple tumors	6/23	
	M/25	16,000 ppm diet x 3 months, then 8000 ppm diet x 15 months (466.7 mg/kg/day[a])	18 months	24 months	subcutaneous	fibromas and fibrosarcomas	21/24 ($p<0.025$) all controls	Weisburger et al., 1978
					other	multiple tumors	8/24 ($p<0.025$) pooled controls only	
Rat/f344	M/20	0	104 weeks	104 weeks	subcutaneous tissue of integumentary system	fibroma	0/20	NCI, 1979
					multiple organs	sarcomas, fibrosarcomas, angiosarcomas, and osteo-sarcomas	0/20	
					multiple organs or tunica vaginalis	mesothelioma	0/20	

TABLE 5-1 (cont.)

Species/ Strain	Sex/ Number	Dose/Schedule	Duration of Treatment	Duration of Study	Target Organ	Tumor Type	Tumor Incidence (P Value)	Reference
Rat/F344	M/50	3000 ppm diet (150 mg/kg/day[a])	104 weeks	104 weeks	subcutaneous tissue of integumentary system	fibroma	28/50 (p<0.001)	NCI, 1979
					multiple organs	sarcomas, fibrosarcomas, angiosarcomas, and osteo-sarcomas	15/50 (p=0.003)	
					multiple organs or tunica vaginalis	mesothelioma	17/50 (p=0.001)	
Rat/F344	M/50	6000 ppm diet (300 mg/kg/day[a])	101 weeks[c]	101 weeks	subcutaneous tissue of integumentary system	fibroma	27/49 (p<0.001)	NCI, 1979
					multiple organs	sarcomas, fibrosarcomas, angiosarcomas, and osteo-sarcomas	37/49 (p<0.001)	
					multiple organs or tunica vaginalis	mesothelioma	9/49 (p=0.036)	
Rat/F344	F/20	0	104 weeks	104 weeks	mammary gland	fibroadenomas	6/20	NCI, 1979
					urinary bladder	carcinoma or papilloma	0/20	
					spleen	sarcomas, angiosarcomas, and osteo-sarcomas	0/20	
					multiple organs	sarcomas, fibrosarcomas, angiosarcomas, and osteo-sarcomas	0/20	

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TABLE 5-1 (cont.)

Species/ Strain	Sex/ Number	Dose/Schedule	Duration of Treatment	Duration of Study	Target Organ	Tumor Type	Tumor Incidence (P Value)	Reference
Rat/F344	F/50	3000 ppm diet (150 mg/kg/day[a])	104 weeks	104 weeks	mammary gland	fibroadenomas	20/50	NCI, 1979
					urinary bladder	carcinoma or papilloma	10/45 (p=0.018)	
					spleen	sarcomas, angiosarcomas and osteo-sarcomas	9/49 (p=0.036)	
					multiple organs	sarcomas, fibrosarcomas, angiosarcomas, and osteo-sarcomas	3/50	
Rat/F344	F/50	6000 ppm diet (300 mg/kg/day[a])	104 weeks	104 weeks	mammary gland	fibroadenomas	35/49 (p=0.002)	NCI, 1979
					urinary bladder	carcinoma or papilloma	22/47 (p<0.001)	
					spleen	sarcomas, angiosarcomas and osteo-sarcomas	12/49 (p=0.01)	
					multiple organs	sarcomas, fibrosarcomas, angiosarcomas, and osteo-sarcomas	21/49 (p<0.001)	
Rat/F344	M/30	0	73 weeks	93 weeks	skin	fibroma	1/27	Hecht et al., 1982
					spleen	fibroma	0/27	
					mammary	fibroadenoma	0/27	
					peritoneum	sarcoma	0/27	

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TABLE 5-1 (cont.)

Species/ Strain	Sex/ Number	Dose/Schedule	Duration of Treatment	Duration of Study	Target Organ	Tumor Type	Tumor Incidence (P Value)	Reference
Rat/F344	M/30	4 g/kg diet (62 mg/ rat/day[d] = 137 mg/kg/ day, body weight = 0.454 kg)	73 weeks	93 weeks	skin	fibroma	25/30	Hecht et al., 1982
					spleen	fibroma	10/30	
					mammary	fibroadenoma	11/30	
					peritoneum	sarcoma	9/30	
Mouse/albino CD-1	M/25	0, matched controls	18 months	21 months	abdominal viscera	vascular hemangio-sarcoma and hemangiomas	0/14	Weisburger et al., 1978
	M/99	0, pooled controls	18 months	21 months	abdominal viscera	vascular hemangio-sarcoma and hemangiomas	5/99	Weisburger et al., 1978
Mouse/albino CD-1	M/25	16,000 ppm diet x 3 months, then 8000 ppm x 15 months (1213 mg/kg/day[b])	18 months	21 months	abdominal viscera	vascular hemangio-sarcomas and hemangiomas	5/14 ($p<0.025$) all controls	Weisburger et al., 1978
	M/25	32,000 ppm diet x 3 months, then 16,000 ppm x 15 months (2427 mg/kg/day[b])	18 months	21 months	abdominal viscera	vascular hemangio-sarcomas and hemangiomas	9/11 ($p<0.025$) all controls	Weisburger et al., 1978
Mouse/albino CD-1	f/25	0, matched controls	18 months	21 months	abdominal viscera	vascular hemangio-sarcomas and hemangiomas	0/15	Weisburger et al., 1978
	f/102	0, pooled controls	18 months	21 months	abdominal viscera	vascular hemangio-sarcomas and hemangiomas	9/102	Weisburger et al., 1978
	f/25	16,000 ppm diet x 3 months, then 8000 ppm x 15 months (1213 mg/kg/day[b])	18 months	21 months	abdominal viscera	vascular hemangio-sarcomas and hemangiomas	5/18 ($p<0.05$) pooled or matched controls	Weisburger et al., 1978

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TABLE 5-1 (cont.)

Species/ Strain	Sex/ Number	Dose/Schedule	Duration of Treatment	Duration of Study	Target Organ	Tumor Type	Tumor Incidence (P Value)	Reference
Mouse/albino CD-1	F/25	32,000 ppm diet x 3 months, then 16,000 ppm x 15 months (2427 mg/kg/day[b])	18 months	21 months	abdominal viscera	vascular hemangio-sarcomas and hemangiomas	9/21 ($p<0.025$) all controls	Weisburger et al., 1978
Mouse/B6C3F1	M/20	0	103 weeks	103 weeks	all sites	hemangio-sarcomas	1/19	NCI, 1979
	M/50	1000 ppm diet (130 mg/kg/day[b])	103 weeks	103 weeks	all sites	hemangio-sarcomas	1/50	NCI, 1979
	M/50	3000 ppm diet (390 mg/kg/day[b])	102 weeks	103 weeks	all sites	hemangio-sarcomas	10/50	NCI, 1979
Mouse/B6C3F1	F/20	0	103 weeks	103 weeks	liver	hepatocellular carcinomas or adenomas	0/20	NCI, 1979
	F/50	1000 ppm diet (130 mg/kg/day[b])	103 weeks	103 weeks	liver	hepatocellular carcinoma or adenomas	4/49	NCI, 1979
	F/50	3000 ppm diet (390 mg/kg/day[b])	103 weeks	103 weeks	liver	hepatocellular carcinoma or adenomas	13/50 ($p<0.007$)	NCI, 1979

[a]Assuming rats consume 5% of their body weight/day as food

[b]Assuming mice consume 13% of their body weight/day as food

[c]All animals died after this duration of treatment.

[d]Reported by Hecht et al., 1982

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the 18-month treatment period, rats were maintained for an additional 6 months on the control diet. A complete gross necropsy was done on all animals that died after 6 months on test or were killed at the end of the study (24 months), with major organs, tumors and abnormal tissues being analyzed histologically. Matched and pooled controls were used for comparison. The incidence of subcutaneous fibromas and fibrosarcomas was most dramatically elevated ($p<0.025$) in both dose groups when compared with matched and pooled controls (0/16, 18/111, 18/23 and 12/24 in matched, pooled controls, low and high-dose groups, respectively). The incidence of multiple tumors (simultaneous occurrence of fibromas or fibrosarcomas, pituitary adenomas, adrenal adenoma or transitional cell carcinoma of the bladder) was higher ($p<0.025$) in high-dose rats (8/24) when compared with pooled controls (14/111). Transitional-cell carcinoma of the bladder showed a nonsignificant increase with increased dose (0/16, 5/111, 3/23, 4/24 for matched, pooled controls, low and high-dose groups, respectively).

Hecht et al. (1982) demonstrated the carcinogenicity of o-toluidine•HCl by dietary administration to F344 rats in a study designed to compare the carcinogenicity of the parent compound and one of its metabolites, o-nitrosotoluene. Groups of 30 male rats were fed diets containing 0 or 4 g o-toluidine•HCl/kg feed for 72 weeks. After an observation period of 20 weeks, all surviving animals were killed. On histopathological examination, a number of tumors were observed in treated rats. Incidences of skin fibroma were 1/27 and 25/30 in the control and treated groups, respectively. Incidences of mammary fibroadenoma were 0/27 and 11/30 in the control groups and treated groups, respectively. Incidences of spleen fibroma were 0/27 and 10/30 in the control and treated groups, respectively. Incidences of sarcomas of the peritoneum were 0/27 and 9/30, respectively.

No p-values for comparison with controls were provided. Other tumors evaluated were liver hepatomas and adenomas, bladder papillomas and carcinomas and Leydig testicular tumors. No p-values for comparison with controls were provided, but these latter tumors were not induced by o-toluidine·HCl. o-Nitrosotoluidine appeared to increase the incidences of liver hepatomas and bladder papillomas.

The carcinogenic effect of o-toluidine·HCl, administered in the diet for 102-103 weeks at 1000 or 3000 ppm (mg/kg diet), was tested in groups of 50 male and 50 female B6C3F1 mice (NCI, 1979). Gross and microscopic examination of major tissues and organs and all gross lesions was performed on all mice found dead during the study or sacrificed after 102-103 weeks. Mean body weights of both dose groups of male and female mice were depressed in comparison with controls. Statistically significant increases in the number of hepatocellular carcinomas or adenomas were noted in treated female mice [0/20, 4/49 and 13/50 ($p=0.007$) for control, low and high-dose groups, respectively]. Male mice in the high-dose group had an increased incidence of hemangiosarcomas at all sites (10/50) when compared with controls (1/19).

Groups of 25 male and 25 female albino CD-1 (HaM/ICR derived) mice were fed o-toluidine·HCl in the diet at two dose levels (Weisburger et al., 1978). The high-dose groups received a 32,000 mg/kg diet for 3 months and then a 16,000 mg/kg diet for an additional 15 months. The low-dose group received a 16,000 mg/kg diet for 3 months and then 8000 mg/kg for 15 additional months. Both groups were maintained for 3 months on control diets after the 18-month treatment period. Gross necropsy and histology of major organs, tumors and abnormal tissues was performed on all animals that died after 6 months on test or were killed at the end of the 21-month study period. In both male and female mice, significant incidences ($p<0.025$) of

hemangiosarcomas and hemangiomas occurred in viscera of the abdomen. The incidence of this type of tumor was 0/14, 5/99, 5/14 and 9/11 in males (for matched control, pooled control, low and high-dose groups, respectively) and 0/15, 9/102, 5/18 and 9/21 in females in the four groups, respectively (Weisburger et al., 1978). [Data presented by Weisburger et al. (1978) were previously introduced in two abstracts by Russfield et al. (1973a,b).]

IARC (1982a) described two limited studies in rabbits, guinea pigs and rats in which a high incidence of papillomas of the bladder developed following s.c. administration of o-toluidine (Morigami and Nisimura, 1940; Santini et al., 1941). Insufficient detail and data were provided in these studies for IARC (1982a) to evaluate them. Morigami and Nisimura (1940) also applied a 0.5% solution of o-toluidine to the skin of rats on alternate days for a nonspecified duration. They observed changes in the bladder epithelium, which included hemorrhage, atrophy and papilloma. The number of animals and incidence of papillomas were not reported.

A number of human case reports have described bladder cancers in workers of the dyestuff industry (Case et al., 1954a,b; Oettel, 1967; Khlebnikova et al., 1970). Exposure of workers to o-toluidine can be inferred since it is used in the production process of aniline dyes. In these studies, workers were additionally exposed to other potential bladder carcinogens (i.e., benzidine, 2-naphthylamine) and little information was available on person-years of exposure specifically to o-toluidine. Oettel (1967) reported 21 cases of bladder papillomas or carcinomas in workers exposed to toluidine and aniline. As a result of the inadequacies of the available data, the case reports of workers in the dyestuff industry cannot be used to positively substantiate an association between bladder cancer and exposure to o-toluidine.

m-Toluidine has been tested for carcinogenicity in male rats and male and female mice, and increased the incidence of liver tumors in male mice at the low dosage level (Table 5-2) (Weisburger et al., 1978). Groups of 25 male Charles River rats were fed diets containing m-toluidine·HCl for 18 months. The low-dose level consisted of 3 months on an 8000 ppm diet followed by 15 months on a 4000 ppm diet. The high-dose level consisted of 3 months on a 16,000 ppm diet, followed by 15 months on an 8000 ppm diet. Matched and pooled control groups were fed a standard diet for 18 months. Following treatment, all groups were maintained on a standard diet for 6 months. Necropsies were performed as described below for mice. No increase in tumor incidence was reported for any tissues in rats at these dose levels.

In the same study, groups of 25 male and 25 female CD-1 mice were fed diets containing m-toluidine for 18 months. Male mice were given a diet containing 16,000 or 32,000 ppm m-toluidine for 5 months, followed by 13 months on a 4000 or 8000 ppm diet, respectively. Female mice were given a diet containing 16,000 or 32,000 ppm m-toluidine for 5 months, followed by 13 months on an 8000 or 10,000 ppm diet, respectively. Matched and pooled controls were fed a standard diet for 18 months. Following treatment, all animals were maintained on a standard diet during an observation period of 3 months. A complete gross necropsy was done on all animals that died after 6 months on test or were killed at the end of the study (21 months), with major organs, tumors and abnormal tissues being analyzed histologically. No increase in tumor incidence in female mice occurred at these dose levels. Male mice were observed to have a significantly ($p<0.025$) increased incidence of hepatomas at the low dosage level only when compared with all pooled controls. The incidences of hepatoma were 1/18, 7/99, 4/16 and 1/16 in matched controls, pooled controls, low and high-dose groups, respectively.

TABLE 5-2

Summary of Oral Carcinogenicity Data for m-Toluidine•HCl[a]

Species/ Strain	Sex/ Number	Dose/Schedule	Duration of Treatment	Duration of Study	Target Organ	Tumor Type	Tumor Incidence (P Value)
Mouse/albino CD-1	M/25	0, matched control	18 months	21 months	liver	hepatoma	1/18
	M/99	0, pooled control	18 months	21 months	liver	hepatoma	7/99
	M/25	16,000 ppm diet x 5 months, then 4000 ppm x 13 months (953 mg/kg/day[b])	18 months	21 months	liver	hepatoma	4/16 ($p<0.025$)
	M/25	32,000 ppm diet x 5 months, then 8000 ppm x 13 months (1907 mg/kg/day[b])	18 months	21 months	liver	hepatoma	1/16

[a]Source: Weisburger et al., 1978

[b]Assuming mice consume 3% of their body weight/day as food

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p-Toluidine•HCl has been tested for carcinogenicity in male rats and male and female mice, and increased the incidence of hepatoma in mice only (Table 5-3) (Weisburger et al., 1978). Groups of 25 male Charles River rats were maintained on diets containing 1000 or 2000 ppm p-toluidine•HCl for 18 months. Groups of 25 male and 25 female CD-1 mice were maintained on low or high-dose diets containing 1000 or 2000 ppm p-toluidine•HCl for 6 months, followed by 12 months on a 500 ppm or 1000 ppm diet, respectively. Simultaneous and pooled control animals were maintained on a standard diet for 18 months. Animals were observed and analyzed histologically as in the m-toluidine study. No increase in tumor incidence was reported for male rats at these dose levels. Treated male mice were observed to have a statistically significant ($p<0.025$) increase in hepatomas when compared with controls. The incidences of hepatoma in matched controls, pooled controls, low and high-dose groups were 3/18, 7/99, 8/17 and 9/18, respectively. Female mice treated with the high dose were observed to have a statistically significant ($p<0.025$) increase in hepatoma only when compared with pooled controls. The incidences of hepatoma in matched controls, pooled controls, low and high-dose groups of female mice were 0/20, 1/102, 2/21 and 3/17, respectively.

5.2. MUTAGENICITY

There have been a number of studies investigating the genotoxicity of o-, m- and p-toluidine (Tables 5-4, 5-5 and 5-6). o-Toluidine has been tested and shown not to be mutagenic in the reverse mutation assay using histidine dependent strains of Salmonella typhimurium. These negative results were obtained both with and without the addition of a mammalian metabolic activation system. The only positive mutagenic response obtained with S. typhimurium was in the assay performed by Nagao et al. (1978) in

TABLE 5-3

Summary of Oral Carcinogenicity Data for p-Toluidine·HCl[a]

Species/ Strain	Sex/ Number	Dose/Schedule	Duration of Treatment	Duration of Study	Target Organ	Tumor Type	Tumor Incidence (P Value)
Mouse/albino CD-1	M/25	0, matched control	18 months	21 months	liver	hepatoma	3/18
	M/99	0, pooled control	18 months	21 months	liver	hepatoma	7/99
	M/25	1000 ppm diet x 6 months, then 500 ppm x 12 months (86.7 mg/kg/day[b])	18 months	21 months	liver	hepatoma	8/17 ($p<0.025$) pooled controls
	M/25	2000 ppm diet x 6 months, then 1000 ppm x 12 months (173.3 mg/kg/day[b])	18 months	21 months	liver	hepatoma	9/18 ($p<0.025$) matched and pooled controls
Mouse/albino CD-1	F/25	0, matched controls	18 months	21 months	liver	hepatoma	0/20
	F/102	0, pooled controls	18 months	21 months	liver	hepatoma	1/102
	F/25	1000 ppm diet x 6 months, then 500 ppm x 12 months (86.7 mg/kg/day[b])	18 months	21 months	liver	hepatoma	2/21
	F/25	2000 ppm diet x 6 months, then 1000 ppm x 12 months (173.3 mg/kg/day[b])	18 months	21 months	liver	hepatoma	3/17 ($p<0.025$) pooled controls

[a]Source: Weisburger et al., 1978

[b]Assuming mice consume 13% of their body weight/day as food

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TABLE 5-4

Mutagenicity of o-Toluidine

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Reference
Reverse mutation	S. typhimurium TA1538	plate incorporation	50, 100 µg/plate	± rat liver S-9	-	Garner and Nutman, 1977
Reverse mutation	S. typhimurium TA1535, TA1537, TA1538, TA98, TA100	plate incorporation	1000 µg/plate	± rat liver S-9	-	Simmon, 1979a
Reverse mutation	S. typhimurium TA100, TA98, TA1537	plate incorporation	NR	+ rat liver S-9 or + mouse liver S-9	-	Zimmer et al., 1980
Reverse mutation	S. typhimurium TA100, TA98, TA1537, TA1535	plate incorporation	10 mg/plate	± rat liver S-9	-	McCann et al., 1975
Reverse mutation	S. typhimurium TA98, TA100	plate incorporation	0.03-30 µmole/plate	± rat liver S-9	-	Florin et al., 1980
Reverse mutation	S. typhimurium TA1535, TA1538	plate incorporation	250 µg/plate	± rat liver S-9	-	Rosenkranz and Poirier, 1979
Reverse mutation	S. typhimurium TA1538	plate incorporation	100 µg/plate	± rat liver S-9	-	Ferretti et al., 1977
Reverse mutation	S. typhimurium TA98, TA100	plate incorporation	50-1000 µg/plate	± rat liver S-9	-	Tanaka et al., 1980
Reverse mutation	S. typhimurium TA98	plate incorporation	50 µg/plate	± rat liver S-9	-	Nagao et al., 1978
Reverse mutation	S. typhimurium TA98	plate incorporation	50 µg/plate	-	-	Nagao et al., 1978
Reverse mutation	S. typhimurium TA98	plate incorporation	50 µg/plate	+ rat liver S-9	-	Nagao et al., 1978
Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537	spot test	3 µmole/plate	± rat liver S-9	-	Florin et al., 1980

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TABLE 5-4 (cont.)

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Reference
DNA modification	*E. coli* pol A⁻, pol A⁺	liquid suspension	0.5 µg/mℓ	-	+	Rosenkranz and Poirer, 1979
DNA modification	*E. coli* pol A⁻, pol A⁺	disc	20 µℓ/plate	-	-	Rosenkranz and Poirer, 1979; Rosenkranz and Liefer, 1980
Prophage induction	*E. coli* K 12	NR	NR	-	+	Galkiewicz et al., 1979
Mitotic recombination	*S. cerevisiae* D3	liquid suspension	0.8%	+ rat liver S-9	-	Simmon, 1979b
DNA damage	Chinese Hamster lung fibroblasts	liquid holding	0.3-10 mM x 2 hours	+ rat liver S-9	-	Zimmer et al., 1980
Cell transformation	leukemia virus infected AKR NIH Swiss mouse embryo cells	plate incorporation	1, 10 µg/mℓ	-	+	Rhim et al., 1974
SCE	Chinese Hamster bone marrow	gavage, intraperitoneal injection	200, 300 mg/kg	NA	+	Neal and Probst, 1983
Sperm head abnormalities	CBA/BALB/C mice	intraperitoneal injection 5 injections/day	0.05-0.5 mg/kg/day	NA	-	Topham, 1980
Testicular DNA synthesis	mice	gavage	200 mg/kg	NA	+	Seller, 1977

NA = Not applicable; NR = Not reported

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TABLE 5-5

Mutagenicity of p-Toluidine

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Reference
Reverse mutation	S. typhimurium TA1538	plate incorporation	50, 100 µg/plate	± rat liver S-9	-	Garner and Nutman, 1977
Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537, TA1538	plate incorporation	1000 µg/plate	± rat liver S-9	-	Simmon, 1979a
Reverse mutation	S. typhimurium TA98, TA100, TA1537	plate incorporation	NR	+ rat liver S-9, ± mouse liver S-9	-	Zimmer et al., 1980
Reverse mutation	S. typhimurium TA100, TA1535, TA1537	spot test	3 µmole/plate	+ rat liver S-9	-	Florin et al., 1980
Reverse mutation	S. typhimurium TA100	plate incorporation	0.03-30 µmole/plate	+ rat liver S-9	-	Florin et al., 1980
Reverse mutation	S. typhimurium TA1535, TA1538	plate incorporation	250 µg/plate	+ rat liver S-9	-	Rosenkranz and Poirer, 1979
DNA modification	E. coli pol A⁻	liquid suspension	5 µg/ml	+ rat liver S-9	-	Rosenkranz and Poirer, 1979
DNA modification	E. coli pol A⁻, pol A⁺	disc	250 µg/plate	-	-	Rosenkranz and Poirer, 1979
Mitotic recombination	S. cerevisiae D3	liquid suspension	0.5%	± rat liver S-9	-	Simmon, 1979b
Mitotic crossing over	S. cerevisiae D3	liquid suspension	1 mg/ml	-	+	Mayer, 1977
DNA damage	Chinese Hamster lung fibroblasts	liquid holding	1.0-10.0 mM x 2 hours	± rat liver S-9	-	Zimmer et al., 1980
Testicular DNA synthesis	mice	gavage	200 mg/kg	NA	+	Seiler, 1977

NA = Not applicable; NR = Not reported

TABLE 5-6

Mutagenicity of m-Toluidine

Assay	Indicator Organism	Application	Concentration or Dose	Activation System	Response	Reference
Reverse mutation	S. typhimurium TA1538	plate incorporation	50, 100 µg/plate	± rat liver S-9	-	Garner and Nutman, 1977
Reverse mutation	S. typhimurium TA98, TA100, TA1537	plate incorporation	NR	± rat liver S-9, ± mouse liver S-9	-	Zimmer et al., 1980
Reverse mutation	S. typhimurium TA98, TA100, TA1535, TA1537	spot test	3 µmole/plate	± rat liver S-9	-	Florin et al., 1980
Testicular DNA synthesis	mice	gavage	200 mg/kg	NA	-	Seller, 1977

NA = Not applicable; NR = Not reported

which norharman (9H-pyridol[3,4-b]indole) was added to the assay system (the mechanism by which norharman facilitates the mutagenicity of other compounds is not known). In addition, Tanaka et al. (1980) reported that ether extracts of urine from rats given an oral dose of o-toluidine were mutagenic in S. typhimiuium only in the presence of mammalian metabolic activation; however, the specific chemical species in the urine responsible for this mutagenic response was not identified.

In other assay systems o-toluidine has produced mixed results. In the absence of an activation system, o-toluidine has produced postive results in the selective inhibition of growth in DNA repair deficient strains of Escherichia coli when assayed in liquid media (Rosenkranz and Poirer, 1979), but not when the compound was allowed to diffuse into the media from filter discs (Rosenkranz and Poirer, 1979; Rosenkranz and Liefer, 1980). In another assay using E. coli K12, o-toluidine stimulated the induction of prophage (Galkiewicz et al., 1979). In eukaryotic systems o-toluidine has caused cell transformations in virus-infected mouse cells in culture, and SCE in hamster bone marrow cells following in vivo exposure (Rhim et al., 1974; Neal and Probst, 1983). Also following in vivo exposure of mice to o-toluidine, thymidine incorporation into testicular DNA was inhibited (Seiler, 1977). Other assays in eukaryotic systems have failed to demonstrate that o-toluidine produces mitotic recombination in yeast (Simmon, 1979b), DNA breaks in cultured mammalian cells (Zimmer et al., 1980) or, following in vivo exposure of mice, morphologic changes in sperm cells (Seiler, 1977). Although not positive in all assays, o-toluidine has demonstrated genotoxicity in both prokaryotic and eukaryotic organisms.

p-Toluidine has also been studied extensively for genotoxicity (see Table 5-5). In assays measuring reverse mutations in S. typhimurium (both

with and without the addition of an activation system), inhibition of growth in DNA repair deficient strains of E. coli, mitotic recombination and cross-over in the yeast, Saccharomyces cerevisiae, and DNA breaks in cultured mammalian cells, p-toluidine has failed to produce positive responses. Only in the assay by Seiler (1977), in which mice were given p-toluidine by gavage and thymidine incorporation in testicular DNA was measured, was a positive response detected (inhibition of DNA synthesis). Since decreased thymidine incorporation can be caused by many mechanisms, there is no clear evidence that p-toluidine is genotoxic.

m-Toluidine has been studied only to a limited extent for genotoxicity (see Table 5-6). In assays of reverse mutations in S. typhimurium (both with and without the addition of a mammalian metabolic activation system), and thymidine incorporation in the testicular DNA of mice, m-toluidine has failed to produce a positive response. Assays of m-toluidine in other test systems have not been located in the available literature.

5.3. TERATOGENICITY

Pertinent data regarding the teratogenicity of o-, m- and p-toluidine were not located in the available literature.

5.4. OTHER REPRODUCTIVE EFFECTS

Topham (1980) reported the absence of sperm head abnormalities in CBA/BALB/c mice given five i.p. injections totaling 0.05-0.5 mg o-toluidine/kg.

Evidence of transplacental migration of o-toluidine or its metabolites was found in a Russian abstract. Golub et al. (1974) administered 4-5 s.c. injections (2 mg total) to pregnant BALB/c mice during the last week of gestation, and observed an increased frequency of tumor development in the progeny.

5.5. CHRONIC AND SUBCHRONIC TOXICITY

Ekman and Strombeck (1947) and Strombeck (1946) observed changes in the bladders of rats fed o- or m-toluidine for 91 or 94 days, respectively. A group of 10 rats was given a rice flour and carrot diet for 64 days which supplied 15-24 mg o-toluidine/day, followed by a similar diet supplying 7.5-12 mg o-toluidine/day until death. A group of nine rats was given a similar treatment with m-toluidine. No controls were reported. The rats fed o- and m-toluidine died after 91 and 94 days of treatment, respectively. Mucous membrane metaplasia and epithelial proliferation was observed in the bladders of 3/10 and 6/9 rats fed o- and m-toluidine, respectively.

Ekman and Strombeck (1949) gave groups of 6 male and 6 female rats diets containing various amounts of riboflavin, ascorbic acid and 0 or 0.1% o- and m-toluidine for 135-341 days. Examination of the urinary bladders of these animals showed effects ranging from epithelial metaplasia with cornification and proliferation, "a tendency to form papillomas," to atypical epithelium. These lesions were observed in 10/26 and 7/24 of the bladders of rats given o- and m-toluidine, respectively. Thickening of the bladder mucosal epithelium without proliferation was observed in 2/7 of the bladders in control rats.

The effects observed in a 104-week chronic feeding study performed to assess the carcinogenicity of o-toluidine·HCl in rats and mice in a National Cancer Institute bioassay were primarily neoplastic (NCI, 1979). No compound-related, non-neoplastic effects were reported to result from the chronic feeding of o-, m- or p-toluidine to rats and mice in the carcinogenicity study by Weisburger et al. (1978) (see Section 5.1. for experimental details for these two studies).

Repeated administration of o-toluidine can cause methemoglobinemia, appetite loss and fatigability (U.S. EPA/NIH, 1983).

5.6. OTHER RELEVANT INFORMATION

An i.v. injection of o-, m- or p-toluidine to cats was reported to produce methemoglobin (McLean et al., 1969). Intraperitoneal injection of o-toluidine to mice was reported to produce methemoglobin (Smith et al., 1967). Rats, rabbits and dogs exposed to o-toluidine produced sulfhemoglobin, methemoglobin and increased levels of cytochrome oxidase (Goldstein et al., 1963).

Acute toxicity in terms of LD_{50}s in rats (oral, 670 mg/kg), mice (oral, 520 mg/kg) and rabbits (oral, 840 mg/kg; dermal, 3250 mg/kg) has been reported by NIOSH (1983).

6. AQUATIC TOXICITY

6.1. ACUTE TOXICITY

The LC_{50} of o-toluidine in the golden orfe, Leuciscus idus melanotus, was determined to be 117 mg/ℓ (duration of exposure not reported) (Juhnke and Luedemann, 1978). The concentrations for 0 and 100% mortality in this species were 30 and 178 mg o-toluidine, respectively. Data available in an abstract of a Russian study (Smirnova et al., 1967) indicate that no toxic effects were evident in guppies, Poecilia reticulata, exposed to 200 mg o-toluidine/ℓ. Guppies exposed to 500 mg/ℓ died within 2-4 minutes. Daphnia magna was more sensitive, with a toxicity threshold level of 2 mg o-toluidine/ℓ and death occurring within 8-20 minutes in those exposed to 20 mg/ℓ (Smirnova et al., 1967). The toxicity threshold values for the protozoan, Entosiphon sulcatum, and the bacteria, Pseudomonas putida, were 76.0 and 16.0 mg o-toluidine/ℓ after 72 and 16 hours, respectively (Bringmann and Kuhn, 1980).

6.2. CHRONIC EFFECTS

Pertinent data regarding the chronic effects of toluidine on aquatic organisms were not located in the available literature.

6.3. PLANT EFFECTS

The effects of o-toluidine on algae have been determined in several studies. The toxicity threshold in the green algae, Scenedesmus quadricauda, was reported to be 6.3 mg/ℓ after 7 days of exposure (Bringmann and Kuhn, 1980); however, little toxic sensitivity was reported for this species by Smirnova et al. (1967). Winters et al. (1976) conducted algal lawn growth toxicity tests with blue-green algae, Agmenellum quadruplicatum, green algae, Chlorella autotrophica and estuarine diatoms, Cylindrotheca sp., exposed to m-, o- and p-toluidine. p-Toluidine was the most toxic

isomer for all species tested. In A. quadruplicatum, 100% growth inhibition was produced by 100 µg/plate for m- and o-toluidine, while 10 µg p-toluidine/plate produced the same effect (Winters et al., 1976). C. autotrophica growth was completely inhibited by 10, 10 and 2 mg/plate, respectively, for m-, o- and p-toluidine (Winters et al., 1976, 1977). Growth inhibition was complete in Cylindrotheca sp. at 10, 10 and 2 mg/plate, respectively, for m-, o- and p-toluidine (Winters et al., 1976). p-Toluidine was also effective in causing 100% growth inhibition at 10 µg/plate in four species of blue-green algae, Coccochloris elabens, Eucapsis sp., Agmenellum quadruplicatum and Oscillatoria williamsii (Batterton et al., 1978). Several other species of blue-green algae were less sensitive but all showed 100% growth inhibition at 0.5 mg p-toluidine/ℓ.

6.4. RESIDUES

o-Toluidine was reported to occur at levels as high as 0.8 µg/ℓ, with a mean level of 0.07 µg/ℓ in the Boven Merwede tributary of the Rhine River (Wegman and DeKorte, 1981). In the Ijssel tributary, levels of o-toluidine were as high as 2.4 µg/ℓ but averaged 0.2 µg/ℓ. The maximum concentrations of p-toluidine in the Boven Merwede and Ijssel tributaries were 0.35 and 0.39 µg/ℓ, respectively, with mean values of 0.07 and 0.08 µg/ℓ, respectively. p-Toluidine was detected with much more frequency than o-toluidine (Wegman and DeKorte, 1981).

6.5. OTHER RELEVANT INFORMATION

p-Toluidine injected into sea urchins, Strongylocentrotus purpuratus, was primarily metabolized by acetylation to p-acetotoluidide or excreted as unchanged p-toluidine (Landrum and Crosby, 1981). In a starfish, Pisaster ochraceus, metabolism was not detected but excretion of unchanged p-toluidine occurred.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

The Occupational Safety and Health Administration (OSHA) standard for occupational exposure to o-toluidine requires that concentrations in air not exceed 5 ppm for an 8-hour TWA (NIOSH, 1983).

The American Conference of Governmental Industrial Hygienists (ACGIH) recommends an 8-hour TLV for o-toluidine of 2 ppm for an 8-hour TWA. ACGIH has given o-toluidine an A-2 classification, meaning that this compound is a suspect carcinogen for man. ACGIH has given o-toluidine a SKIN notation, which means that the substance can contribute to the overall exposure by the cutaneous route (ACGIH, 1982). Linch (1974) has suggested a TLV for m- and p-toluidine of 1 ppm, based on biological (urinary) monitoring and their potential to cause chemical cyanosis.

The Food and Drug Administration (FDA) has established a tolerance of 0.1% for p-toluidine in D and C green dye No. 6 (U.S. DHHS, 1982).

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of m-, p- or o-toluidine were not located in the available literature.

8. RISK ASSESSMENT

Sufficient evidence exists to consider o-toluidine an animal carcinogen, and a mutagen in short-term tests. IARC (1982b) has concluded that, although evidence for the carcinogenicity of o-toluidine in humans is equivocal, when considered along with the data regarding carcinogenicity to animals the weight of evidence indicates that the compound is probably carcinogenic to humans.

Three chronic feeding studies in rats and mice have demonstrated the carcinogenicity of the hydrochloride of o-toluidine. The use of the hydrochloride is expected to be of little consequence, as o-toluidine will react with stomach acid to form the hydrochloride. In assessing risk of exposure to o-toluidine, however, the doses expressed as hydrochloride will be converted to the amounts of o-toluidine ingested.

NCI (1979) provided probably the best evidence for o-toluidine carcinogenicity in rats. Groups of 50 male and female F344 rats were fed diets containing 3000 or 6000 ppm o-toluidine·HCl for 2 years. The incidence of subcutaneous fibromas in control, low-dose and high-dose male rats was 0/20, 28/50 and 27/49, respectively. The incidence of mammary gland fibroadenomas in control, low-dose and high-dose female rats was 6/20, 20/50 and 35/49, respectively. The incidence of carcinomas in the urinary bladder of control, low-dose and high-dose female rats was 0/20, 9/45 and 22/47, respectively. A number of other tumors, primarily malignant and involving the spleen, abdominal cavity and scrotum, also occurred at higher incidences among treated groups than among controls. The transformed low and high doses for these animals are 112 and 224 mg o-toluidine/kg/day. These are obtained by the product of the level of o-toluidine·HCl in the diet, the assumed food consumption rate in rats (i.e., 5% of body weight/day), the

molecular weight ratio of o-toluidine/o-toluidine·HCl (i.e., 107.2/143.6= 0.7465), and the ratio of length of exposure/length of experiment.

In a more recent study, Hecht et al. (1982) demonstrated increased incidences of skin fibromas, mammary fibroadenomas, spleen fibromas and peritoneal sarcomas in groups of 30 male F344 rats maintained for 73 weeks on diets containing 4000 ppm o-toluidine·HCl followed by 20 weeks of observation. The skin fibroma response gave the greatest increase in incidences: 25/30 treated versus 1/27 control. The transformed dose is calculated to be 80 mg o-toluidine/kg/day, based on the mean daily dosage of 62 mg o-toluidine·HCl/rat (reported by Hecht et al., 1982), the measured body weight, the molecular weight ratio of o-toluidine/o-toluidine·HCl and the ratio of length of exposure/length of experiment.

Similarly, Weisburger et al. (1978) demonstrated increased incidences of subcutaneous fibromas and fibrosarcomas in groups of 25 male Sprague-Dawley rats ingesting diets containing 8000 ppm for 3 months followed by 4000 ppm o-toluidine·HCl for 15 months (low dose), and 16,000 ppm for 3 months followed by 8000 ppm for 15 months (high dose). Incidences of these tumors were 0/16, 18/111, 18/23 and 21/24 for the matched controls, pooled controls, low-dose group and high-dose group, respectively. The estimated transformed low and high doses for these animals are 130.6 and 261.3 mg o-toluidine/kg/day, assuming that rats consume food at a rate of 5% of their body weight/day and multiplying by the ratios of the molecular weights of o-toluidine/o-toluidine·HCl and the length of exposure/length of experiment.

In addition, both NCI (1979) and Weisburger et al. (1978) demonstrated the carcinogenicity of o toluidine·HCl in mice. In a study by the NCI

(1979), at estimated transformed dosage levels of 97 and 291 mg o-toluidine/kg/day, a statistically significant increased incidence of tumors was observed only for liver tumors in female mice. The incidence of hepatocellular carcinoma and adenoma among female mice was 0/20, 4/49, and 13/70 (p=0.007) in control, low-dose, and high-dose groups, respectively.

In the study by Weisburger et al. (1978), at estimated transformed dosages of 776 and 1553 mg o-toluidine/kg/day, increased incidences of hemangiosarcomas and hemangiomas of the abdominal viscera occurred in both male and female mice. The incidences in treated males, which were higher than those in treated females, were 0/14, 5/99, 5/14 and 9/11 in the matched controls, pooled controls, low-dose group and high-dose group, respectively.

Dose levels for these studies were calculated from dietary levels of o-toluidine·HCl by assuming that mice consume food at a rate of 13% of their body weight/day. The resultant dose as mg o-toluidine·HCl/kg/day was then multiplied by the ratio of the molecular weight of o-toluidine/o-toluidine·HCl and by the ratio of the length of exposure/length of experiment.

Of the carcinogenicity data available for o-toluidine, the dose-response data that will yield the highest carcinogenic potency factor for humans are the data for the skin fibroma response of male F344 rats reported by Hecht et al. (1982). Using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (1980), a carcinogenic potency factor (q_1^*) of 2.404×10^{-1} $(mg/kg/day)^{-1}$ can be derived for humans from these data. The corresponding dose of o-toluidine associated with an increased lifetime cancer risk of 10^{-5} is 4.16×10^{-5} mg/kg/day or 2.91×10^{-3} mg/day for a 70 kg man. Complete data for derivation of the q_1^* are presented in Appendix B.

Weisburger et al. (1978) provided the only available study regarding the carcinogenicity of m-toluidine in laboratory animals. The tumor incidence in this study was slightly elevated in only one dosage group of one sex and species. Tumor incidence was reported as elevated in male albino CD-1 mice, but not in female albino CD-1 mice or male Charles River rats. The low-dose level, 953 mg m-toluidine·HCl/kg/day, is obtained by assuming that mice consumed 13% of their body weight/day of the 16,000 ppm diet for 5 months, followed by the 4000 ppm diet for 13 months. The high-dose level, 1907 mg m-toluidine·HCl/kg/day, is obtained by assuming that mice consumed 13% of their body weight/day of the 32,000 ppm diet for 5 months, followed by the 8000 ppm diet for 13 months. The transformed low and high doses are 705.2 and 1410.4 mg m-toluidine/kg/day, respectively. These are obtained by the product of the dose level of hydrochloride, the molecular weight ratio of m-toluidine/m-toluidine·HCl and the ratio of length of exposure/length of experiment. The incidences of liver hepatomas in male mice were 1/18, 7/99, 4/16 and 1/16 for the matched controls, pooled controls, low-dose group and high-dose group, respectively. The incidence of hepatoma was statistically significantly elevated only at the low dose and only when compared with pooled controls. These data are judged to be an inadequate basis for the assessment of carcinogenic risk from exposure to m-toluidine.

Weisburger et al. (1978) also provided the only available study regarding the carcinogenicity of p-toluidine in laboratory animals. In this study, increased tumor incidences were observed in mice but not rats. The albino CD-1 mice were maintained on two levels of p-toluidine·HCl in their diet for 18 months. The low-dose level, 86.67 mg p-toluidine·HCl/kg/day, is obtained by assuming that mice consumed 13% of their body weight/day of the 1000 ppm diet provided for 6 months, followed by the 500 ppm diet for 12 months. The high-dose level, 173.3 mg p-toluidine·HCl/kg/day, is obtained

by assuming that mice consumed 13% of their body weight/day of the 2000 ppm diet provided for 6 months, followed by the 1000 ppm diet for 12 months. The transformed low and high doses are 55.5 and 111 mg p-toluidine/kg/day, respectively. These are obtained by the product of the dose levels of hydrocloride, the molecular weight ratio of p-toluidine/p-toluidine· HCl and the ratio of length of exposure/length of experiment. The incidences of liver hepatoma were elevated in both sexes, but were statistically significantly higher than matched controls only in males. The incidences of liver hepatoma in male mice were 3/18, 7/91, 8/17 ($p<0.025$) and 9/18 ($p<0.025$) in the matched controls, pooled controls, low-dose group and high-dose group, respectively. According to the IARC (1982b) guidelines, the available data provide limited rather than sufficient evidence of the carcinogenicity of p-toluidine to animals. Because the data are suggestive of carcinogenicity, and because the closely related chemical o-toluidine has been found to be carcinogenic, the data from the Weisburger et al. (1978) chronic oral study in male mice will be used to estimate a carcinogenic potency factor (q_1^*) for humans. Using the linearized multistage model developed by Kenneth Crump and adopted by the U.S. EPA (1980), a carcinogenic potency factor (q_1^*) of 1.893×10^{-1} $(mg/kg/day)^{-1}$ can be derived for humans. The corresponding dose of p-toluidine associated with an increased lifetime cancer risk of 10^{-5} is 5.28×10^{-5} mg/kg/day or 3.70×10^{-3} mg/day for a 70 kg man. Complete data for derivation of the q_1^* are presented in Appendix C.

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APPENDIX A
LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
EPCASR
Chemical Industry Notes

These searches were conducted in May, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 7 and 8th), and the following secondary sources were reviewed:

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Portions of the carcinogenicity section in this profile were adapted from a report [Review of Toxicologic Data in Support of Evaluation for Carcinogenic Potential of Ortho-Toluidine and its Hydrochloride (95-53-4) (636-21-5)] prepared by Syracuse Research Corporation (1983) for the Carcinogen Assessment Group of the U.S. EPA under Contract No. 68-03-3112.

APPENDIX B

Cancer Data Sheet for Derivation of q_1^*

Compound: o-toluidine·HCl

Reference: Hecht et al., 1982

Species, Strain, Sex: Rats, F344, male

Body Weight: 0.454 kg (measured)

Length of Exposure (l_e) = 511 days

Length of Experiment (L_e) = 651 days

Lifespan of Animal (L) = 730 days (assumed)

Tumor Site and Type: skin fibroma

Route, Vehicle: oral, diet (4 g o-toluidine·HCl/kg food)

Experimental Doses or Exposures to o-toluidine·HCl	Transformed Dose mg/kg/day of o-toluidine	Incidence No. Responding/ No. Tested (or Examined)
0	0	1/27
62 mg/rat/day x 511 days	80	25/30

Human $q_1^* = 2.404 \times 10^{-1}$ $(mg/kg/day)^{-1}$ (for o-toludine)

10^{-5} risk level = 4.16×10^{-5} mg/kg/day = 2.91×10^{-3} mg/day (of o-toluidine) for 70 kg man

APPENDIX C

Cancer Data Sheet for Derivation of q_1^*

Compound: p-toluidine•HCl

Reference: Weisburger et al., 1978

Species, Strain, Sex: mice, albino CD-1, male

Body Weight: 0.03 kg (assumed)

Length of Exposure (l_e) = 548 days

Length of Experiment (L_e) = 639 days

Lifespan of Animal (L) = 730 days (assumed)

Tumor Site and Type: liver, hepatoma

Route, Vehicle: oral, diet

Experimental Doses or Exposures to p-toluidine•HCl	Transformed Dose mg/kg/day of p-toluidine	Incidence No. Responding/ No. Tested (or Examined)
0	0	3/18
(1000 ppm x 6 months) + (500 pm x 12 months)	55.5	8/17
(2000 ppm x 6 months) + (1000 ppm x 12 months)	111	9/18

Human $q_1^* = 1.893 \times 10^{-1}$ $(mg/kg/day)^{-1}$ (for p-toluidine)

10^{-5} risk level = 5.28×10^{-5} mg/kg/day = 3.70×10^{-3} mg/day (of p-toluidine) for 70 kg man